PHARMACOLOGY OF THE FAILING HUMAN HEART

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PREFACE

THE development of the intracardiac catheter as a physiological instrument applicable to man has opened up a vast new field of research on the problem of the failing human heart. The heart can be approached directly and its output and haemodynamic behaviour are now subject to more direct observation than ever before. Some older ill-defined concepts of heart failure have been consolidated and many have been discarded as a result of the newer observations. In the Post-graduate Medical School of London, during the past eight years, we have made a systematic study of patients with various forms of heart failure with these new techniques. From time to time we have ventured to report on our findings, but the growth of experience with the technique in our own School and elsewhere has made many of our earlier ideas seem over-simple. We should emulate Fuller Allbright and say that 'any hypothesis propounded is liable to change without notice'. Working hypotheses are made on the basis of known facts and the application of current physiological opinion, but the inexorable development of fresh factual observation and altering conceptions compel parallel changes in outlook. The view previously expressed that primary venous pressure reduction might be largely responsible for determining success or failure of digitalis therapy is no longer acceptable. One attraction of this hypothesis was that it afforded a possible explanation of therapeutic successes and failures: but mere usefulness is no substitute for accuracy and the whole problem is once again in the melting pot Observation is more important than interpretation while hypotheses may be lost, factual observations have been gained and extended and technical progress in more accurate recording of intracardiac pressures has now been added I welcome the invitation of the editors to review the present situation in the light of the new knowledge which is now available.

There is no doubt that in the early days of cardiac catheterization most workers were over-impressed by small changes in output which can now be regarded as devoid of statistical significance. With the use of a somewhat bold technique there was too great a desire to use *all* the available figures and draw whatever conclusions seemed possible. Now that the safety of the procedure has been established and widely accepted we realize from a much wider experience that earlier deductions were being made from too small numbers of observations. A much more critical approach is necessary. Greater numbers of observations will be necessary before many of the outstanding problems can be seen in proper perspective.

The work here reported could never have been done without the loyal co-operation of the department staff and research assistants. I wish to mention particularly Professor E. P. Sharpey-Schafer, Dr. S. Howarth, Dr. Paul Wood, and more recent workers, Drs. Ahmed, Bayliss, Kelly, Reid, Etheridge, and Hyman. Personal contact and free discussion and criticism with Drs. André Cournand, Dickinson Richards, Eugene Stead, J. V. Warren, J. Lenègre, and Lars Werko have helped to mould the opinions expressed. Professors Lenègre and Loubatières kindly put some unpublished data at my disposal.

It is appropriate that this short monograph should be published in the American Lecture Series. The research material has been presented in lectures in various parts of the United States, and I specially wish to acknowledge the honour of giving the following lectures:

Henry Jackson Lecture to the New England Heart Association, 1947.

Guest Lectures to the California Heart Association, 1948

John H. Musser Lecture in Tulane University, New Orleans, 1948.

Thayer Lectures, Johns Hopkins Hospital, Baltimore, 1948

J. McM.

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CHAPTER I

GENERAL IDEAS ON HEART FAILURE

THE idea of depression of cardiac output as a necessary consequence of organic heart disease was courageously banished by Harrison[1] some fifteen years ago. He was willing to accept the evidence, based at that time on somewhat indirect methods of estimation of cardiac output in man, that the output of the heart need not necessarily be low in patients with heart disease even in heart failure. Catheter studies have now established quite clearly that certain types of heart failure may even be associated with a resting cardiac output above the normal level which in a placid, recumbent adult averages about 5·3 litres per minute. Heart failure from the haemodynamic point of view may thus be subdivided into low output and high output types.[2,3]

In the low output group we find those which are the result of intrinsic heart disease such as valvular and ischaemic disease. Hypertensive heart disease also falls into the same category, apparently the mechanical overburdening of the heart by increased arterial resistance plays a part in the production of an ultimate cardiac breakdown of the same type as that seen when the cardiac embarrassment has resulted from distorted or leaking valves.

By contrast the high output type of cardiac failure takes place in conditions which call in the first instance for an increased cardiac output. Such states include:

1. Severe anaemia.
2. Beri-beri.
3. Emphysema.

4. Mechanical overloading of the circulation:
   (*a*) arteriovenous aneurysms;
   (*b*) widespread Paget's disease of bone.

It will be understood that anaemia and emphysema are, for different reasons, accompanied by decreased oxygen-carrying power of the blood, and adequate tissue oxygenation may only be achieved by a more rapid circulation. In the group 4 of the above conditions the circulation is encumbered by an additional 'parasitic' circulation which, by producing a long-term embarrassment, may ultimately lead to failure. All the manifestations which the clinician recognizes as heart failure may appear in this 'high output group'—particularly venous congestion, peripheral oedema, and dyspnoea. *The two groups of heart failure may be* differentiated clinically, as patients with the high output variety usually have warm extremities and full or bounding peripheral pulses. The extrinsic cause of circulatory embarrassment, e.g. anaemia or emphysema, is usually recognizable. The practical importance of recognition of the two groups is that treatment is different. It should be directed to the cause of the failure in the high output types.

When the output of the heart has fallen to a low level in heart failure the clinical picture is different. The extremities tend to be cold and blue and the peripheral pulse small. Occasionally *in extremis* the nose and finger-tips may become cyanotic or even black; central veins like the jugular are engorged while peripheral veins like those at the elbow may contract down to mere threads.

While the sub-division of cardiac failure into these two contrasting haemodynamic types may often be clearly recognizable, it should also be realized that they are not completely and sharply demarcated in all instances.[3] It should be kept in mind that in the more advanced stages of emphysema heart failure, for example, the cardiac output may sometimes be observed to fall below the normal value.[4] It might be thought that thyrotoxicosis would fall into this high output group, but, in our experience, when thyrotoxicosis is accompanied by gross venous congestion

and oedema the output has been low.[8] Experience of this type of failure is limited nowadays by the efficiency of modern antithyroid remedies. In the earlier stages of thyrotoxicosis, however, the cardiac output, as expected, is well above normal. Early manifestations of cardiac failure may make their appearance in the 'low output' group before the resting output has fallen very much and even while the output is still within normal limits. This applies particularly to patients who develop left ventricular failure [redacted] a result of hypertensive or aortic valve disease. In such patients attacks of dyspnoea and pulmonary oedema occur while the output of the heart is normal or even slightly above the normal average. We may imagine that the relatively efficient right heart is driving the enfeebled left ventricle, but the output of the latter is only maintained at the expense of extreme pulmonary vascular engorgement which results in breathlessness.

Depression of the resting cardiac output is therefore absent in the early stages of most forms of heart failure, and significant diminution of cardiac output is only seen in the late stages. It is obvious, however, that in all conditions leading to failure the heart [redacted] *under load* and its capacity to sustain extra work is decreased. It is difficult to define heart failure except in some such terms as follows: *the heart is failing when its capacity to increase output is seriously impaired and when output is only maintained at the expense of a raised venous-filling pressure; the late stages are characterized by an output which is falling below the previous level, with further increase in systemic venous congestion*

The mechanism by which the venous pressure rise takes place is a matter of some interest[9] It [redacted] clearly not a simple back pressure effect, at least in the early stages of cardiac failure, as significant rises in venous pressure are found when the output of the heart [redacted] normal or high. Under these circumstances blood is not accumulating on the venous side of the circulation from failure of the heart to transfer blood into the arteries. An alternative explanation seems to be that physiological mechanisms for the maintenance of an adequate cardiac output come into action and among these adaptations we must postulate a veno-

motor mechanism which raises the venous pressure sufficiently high maintain to the output of the heart at the required level (Fig. 1).

It seems likely that the early rises of venous pressure take place first on exercise. It has been shown that sustained rises of venous pressure following exercise only occur in cardiac patients.[7] In normal subjects the rise in venous pressure in exercise is small and is very quickly restored to normal immediately the exercise ceases.[6, 8] The raised venous pressure of exercise becomes sustained as the diseased heart fails to recover from the strain The beneficial effects of rest in the early stages of heart failure are in keeping with this conception.

Although we shall have little more to say about physical rest as a therapeutic remedy in cardiac failure, it is probably as important in the régime and management as all the other remedies put together. Early warnings of failure, such as nocturnal dyspnoea and inability to walk up hills, may in certain instances be very considerably alleviated if the patient can spend his week-ends in bed. When physical rest to the heart is being considered it is well to remember that the resting output of a normal individual is lower during quiet standing than in complete recumbency.[9] As the patient with nocturnal orthopnoea knows, the optimum position to relieve his heart is sitting on the side of his bed. Rest to the heart at certain critical stages of heart failure is best provided when the patient is propped up or sitting up in a cardiac bed or a high armchair

In addition to the above types of heart failure which are characterized by an overload effect created either by extrinsic factors or intrinsic abnormalities of a *chronic* variety in the valves of the heart or the myocardium, there are other types of heart failure which may result mainly from some more acute intrinsic disease of the heart muscle. These include diphtheritic and rheumatic myocarditis. At the acute phase of such diseases the general trend of opinion is that relatively little may be expected in the way of therapeutic effects from the remedies applicable to more chronic types. The failure which accompanies these special varieties of heart disease has not yet been studied from the

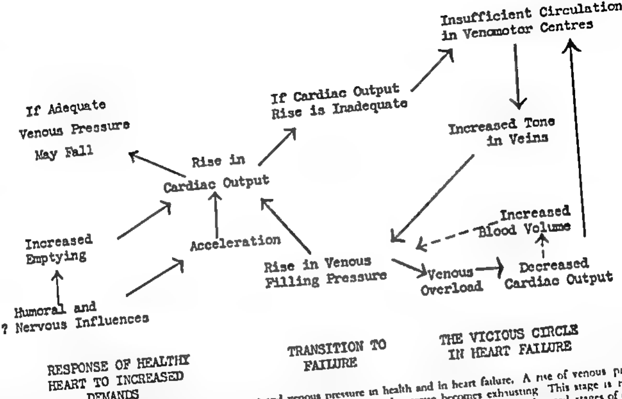

FIG. 1 The relationship between cardiac output and venous pressure in health and in heart failure. A rise of venous pressure does not play much part in increasing the cardiac output in normal subjects until exercise becomes exhausting. This stage is reached more readily in the presence of heart disease, and it is possible that a vicious circle may be created in the advanced stages of cardiac failure, i.e. inadequate cardiac output induces reflexly a rise in venous pressure, but this may overstretch and overload the heart, leading to further failure. (Reproduced from the *American Journal of Medicine*.)

haemodynamic and pharmacological point of view with the newer techniques.

It is important, however, to keep the myocardium strongly in mind throughout our therapeutic approach to cardiac patients. It is only in the immediate responsiveness and ultimate adaptability of the myocardium that our hopes lie for any amelioration in the course of most forms of organic heart disease. The following common types of clinical experience may illustrate the meaning. Manifestations of cardiac failure with pulmonary and systemic venous congestion may appear during the course of acute myocardial infarction. With rest and care these may ultimately clear up and the patient return to useful life for a period of years. The anatomical basis of this recovery is probably 'physiological' hypertrophy of the remaining myocardial fibres. Less dramatically, one may encounter patients with calcified aortic valves or narrow mitral valves who have lived into the sixth and seventh decade before cardiac failure becomes manifest. In many instances we have evidence that the anatomical embarrassment has been present for, perhaps, twenty years, and yet the process of adaptation seems to be complete and compatible with sedentary or moderate work over this long period. Conversely, in those patients with rheumatic heart disease who go rapidly downhill with a progressively severe disablement over a period of five to ten years, post-mortem examination frequently reveals smouldering rheumatic carditis. Similarly, it seems clear that heart failure in thyrotoxicosis is not entirely the result of prolonged tachycardia in such patients but is rather a consequence of some metabolic disturbance in myocardial contractility. It is also a matter for speculation why the heart breaks down ultimately in patients with hypertension. Chronic benign essential hypertension may be well tolerated for decades, and then, without further apparent rise in the systemic arterial pressure, heart failure suddenly supervenes. Myocardial factors in such patients have not yet been convincingly demonstrated anatomically, but there can be little doubt that some other critical event

has occurred turning a simple physiological compensatory hypertrophy into an enlarged dilated failing heart.

Finally, we should emphasize a difference in adaptation to two types of overload. It was shown experimentally by Müller[10] that the isolated mammalian heart could tolerate an increased work load created by a raised minute volume very much better than a similar work load imposed by increased arterial pressure. The normal heart can probably adapt very readily to a demand for increased output up to five times or more the resting normal value. If, however, the output remains constant but the arterial pressure is increased acutely, doubling or trebling the arterial pressure will at once lead to failure. These points may be illustrated again from clinical experience. An acute rise of arterial pressure occurring, for example, in acute nephritis, may be associated with dyspnoea and failure, although the pressure rise is quite a modest one. Conversely, patients with traumatic arterio-venous aneurysms may tolerate large increases of resting cardiac output through many decades. The author has observed one patient who had a femoral arterio-venous communication following a gunshot wound in 1918. He was capable of active work and considerable activity until 1947, when he alarmed his physician by developing auricular fibrillation. At this stage cardiac catheterization was done; there was no venous congestion but the resting cardiac output was 12·1 litres per minute. The patient had apparently tolerated an increased resting output of this order for over thirty years, and in spite of the coincidence of auricular fibrillation did not, even then, develop any manifestations of cardiac embarrassment. A somewhat similar state of affairs is seen in atrial septal defects. In this condition a large volume of blood poured through from the left auricle to the right may be added to the blood returning to the heart via the systemic circulation. The resting output of the right ventricle in such patients may be raised perhaps as high as three times the normal.[11] Yet these subjects are often capable of leading active lives. I have known a young man with this condition who played strenuous football once a week. Increased output then is much less likely

to strain the heart, and it is a less important factor in determining failure than an increased peripheral vascular resistance.

Responses to drugs and other methods of treatment in cardiac failure vary with the differing aetiological varieties of the syndrome. Not only may the response vary from one aetiological group to another, but it may also be dependent upon the stage of failure and perhaps to some extent on the speed of development of cardiac failure in any single aetiological group. Hearts which have ceased to make any response to members of the digitalis series may respond, albeit temporarily, to the administration of theophylline-ethylene-diamine.

THE BEHAVIOUR OF THE FAILING HEART: RESPONSES TO VENESECTION AND MERCURIAL DIURETICS

STARLING'S *law of the heart*. Just before the first World War, Starling studied the factors regulating the output of the isolated mammalian heart He established what was called the Law of the Heart, which indicated that the output of the heart was determined by the diastolic fibre length.[12] The longer the myocardial fibres, within physiological limits, the greater the contractile response. With a greater inflow of blood into the isolated heart during diastole the fibres of the heart chambers were stretched and the output per beat was correspondingly increased. The venous inflow in turn was largely dependent upon the venous filling pressure. From the data he obtained Starling was therefore able to show a fairly direct linear relationship between venous filling pressure and cardiac output (Fig 2). There was, however, a little doubt about the exact part played by the pressure factor itself in determining fibre length Starling himself concluded that diastolic tension within the ventricle was not the deciding factor, but the optical methods of registering diastolic pressures which Starling used were later subjected to criticism by Wiggers. Wiggers concluded that strength of the ventricular beat was dependent on very small changes in diastolic tension, the recognition of which was not possible by the methods which Starling had used[13] Wiggers' investigation seemed to establish the influence of filling pressure in determining the output of the heart. In recent years the general applicability of Starling's Law to the mammalian heart *in situ* has been called in question, and from the work of Warren and Stead[14] it is quite clear that Starling's Law no longer holds the dominant position in physiological

integration of the circulation once ascribed to it. The output of the normal heart is certainly subject to nervous and hormonal

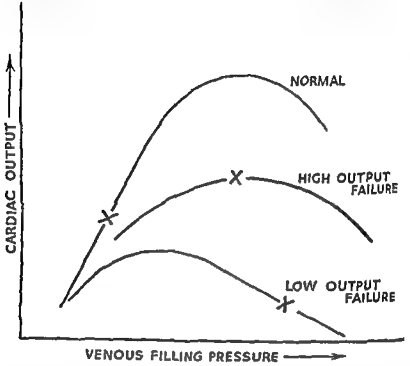

FIG. 2 Hypothetical Starling curves in normals, high output failure and low output failure The normal heart may increase its output to a high level with increased venous filling pressure In anaemic heart failure the high output is probably maintained at least in part by an increased filling pressure Further increase of this filling pressure may lead to a decrease in output In severe low output heart failure the heart has in most instances passed to a stage at which increments of pressure lead to decreases in cardiac output. The response is usually a fall in output with increased venous return and, conversely, venesection may lead to improvement in output. (Reproduced from *Clinical Science*)

control and regulation. The influence of venous filling pressure may only play a small and rather subsidiary part in the regulation of cardiac output within the physiological range in normal intact man.

There are, none the less, many circumstances in which the

influence of venous filling pressure on the heart in man may be clearly demonstrated. The most important of these are:

1. The influence of posture. In the upright position the venous return to the heart is made more difficult and the pressure in the great veins close to the heart falls. As a result of this fall in filling pressure the output of the heart declines. In a normal resting recumbent adult the output of the heart may be 5·3 litres per minute, falling to 4 litres per minute on quiet standing.[9]

2. Cournand and his colleagues[13] have shown that the pulse pressure, and therefore presumably the stroke output, of the right ventricle varies with the respiratory cycle in a manner consistent with Starling's Law.

3. The decreased cardiac output of haemorrhagic shock responds quite dramatically to intravenous saline or blood infusion, the output rising with increases in venous filling pressure.[16]

4. In some normal subjects clearly defined rises of cardiac output with increases of venous filling pressure produced by saline infusion may be seen.[9]

Starling's Law is a special application of a fundamental physiological property of striated muscle. While it may be concealed by many other physiological adaptative mechanisms of a nervous and humoral variety it almost certainly plays a role in the adaptation of the heart to disease. When the output of the diseased or embarrassed heart tends to fall from the optimum there is increased residual blood in diastole, the myocardial fibres are at once stretched, and this stretching influence is probably the stimulus to enlargement and hypertrophy.[11] In the presence of circulatory failure, whether of cardiac origin or peripheral (haemorrhagic shock), Starling's Law may play a dominant physiological role. For example, in pericardial effusion the external pressure of fluid on the heart may render venous filling inadequate.[15] A raised venous pressure in such instances can be regarded as a 'compensatory' mechanism.[15] Lowering of such raised venous pressure may be harmful while raising the venous

filling pressure may help to maintain adequate cardiac filling and therefore adequate cardiac output. Transfusion is necessary in the treatment of haemorrhagic shock to raise the low filling pressure and thereby the cardiac output. In many instances of circulatory failure with high cardiac output (anaemia, etc.), a raised venous pressure possibly plays a part in maintaining the output of the heart at a necessarily high level[20] (Fig. 2).

Overload failure. Using the isolated heart of a dog, Starling showed that, while increases in venous filling pressure raised the cardiac output, this relationship only held over a certain physiological range. If the venous pressure was raised to a point at which the heart began to be overstretched, then no further rise in output would take place, while still further increases in venous filling pressure would be accompanied by a definite fall in cardiac output.[12] Starling had created a type of cardiac failure which could be called 'overload' failure (Fig 2).

We have at present reasonable grounds for believing that many forms of cardiac failure in man are the result of a somewhat similar mechanism The evidence that the failing human heart behaves as though it were overloaded consists of the following:

1. Transfusion, if given too rapidly to the anaemic heart, may induce serious failure.[21] In such instances the venous filling pressure was observed to rise while the cardiac output simultaneously fell (Fig. 3). *Attacks of left heart failure have also followed* intravenous infusions in hypertensive and mitral disease.[21a]

2. Exercise which, in normals, is accompanied by a slight rise in venous pressure, is accompanied by a considerable rise of venous pressure in patients with heart failure,[1] but in such patients the output of the heart may fall rather than increase.[22]

3. The increased central venous pressure of recumbency may induce left heart failure within a few hours This may be the explanation of attacks of paroxysmal nocturnal orthopnoea.

4 The reduction of venous filling pressure may be accompanied by clinical improvement and relief of cardiac failure.[23]

(*a*) This may be the mechanism of relief in the upright position in attacks of paroxysmal nocturnal orthopnoea.

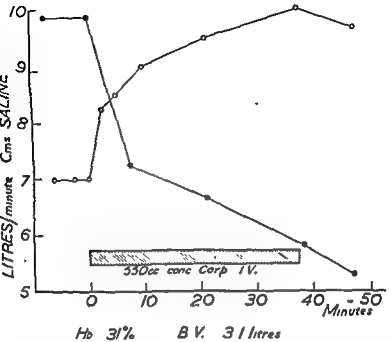

FIG. 3 The effect of transfusion in anaemic heart failure. A patient with severe hypochromic anaemia was given a transfusion of 550 c c. of concentrated corpuscles The high right auricular pressure (open circles) was raised still further and the cardiac output (dots) fell from nearly 10 litres per minute to 5 litres per minute. A severe attack of cardiac failure followed with dyspnoea and pulmonary congestion (Reproduced from the *Lancet*)

(*b*) The dramatic relief which is sometimes given by venesection may be explicable in terms of removing a cardiac overload.

Venesection is a time-honoured emergency remedy in cardiac failure. To be effective it must amount to at least 300 c.c., and perhaps 500 to 600 c.c. is best. Bleeding of this magnitude will be accompanied by a considerable reduction in venous pressure, and it has now been well established that, accompanying the induced fall in venous pressure, the cardiac output may rise considerably[23],

[24, 25] (Fig. 4). The simplest hypothesis to account for the effect of venesection is based on the conception that the failing heart

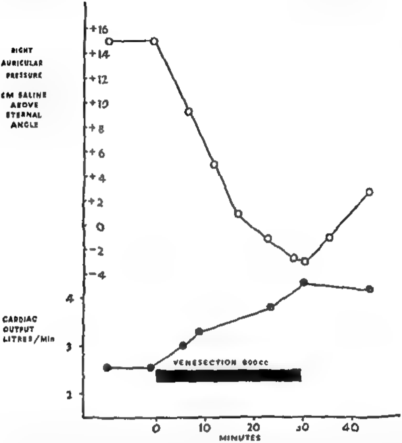

Fig. 4 The effect of venesection in hypertensive cardiac failure During the withdrawal of blood, pressure in the right auricle fell and the cardiac output steadily climbed from 2 6 to 4 3 litres per minute Simultaneously there was a fall in arterial pressure (Reproduced from *Clinical Science*)

is overloaded in the manner suggested by Starling. Relief of venous over-distension is accompanied by steady improvement in cardiac output.

Another factor, however, is involved in venesection. Although the cardiac output increases, the arterial pressure in these instances

is found to fall as the venesection proceeds.[23] This means that venesection is accompanied by peripheral vasodilatation. The heart may thus be unloaded from both ends—venous and arterial. Whatever the detailed explanation may be, it is difficult to avoid the thought that simple mechanical relief of an overstretched myocardium is the major factor involved in bringing about the striking relief which may follow venesection.

Somewhat similar effects may be achieved, as already indicated, by the upright position and the way in which the orthopnoeic patient with left ventricular failure treats himself by adopting this position merits detailed study. Pneumatic cuffs round the thighs may dam back blood in the veins of the legs and also produce some relief: the efficacy of such measures in increasing the cardiac output has been shown by the writer and his colleagues.[23] Central venous pressure may be reduced 6 or 7 cm. saline by the application of thigh cuffs and the cardiac output may rise significantly.

The beneficial action of venesection is probably best seen in hypertensive and ischaemic heart disease. In these conditions we probably see the purest form of myocardial overloading which may be relieved by adjustments of filling pressure. In valvular heart disease, where, for example, the aortic and mitral valves are narrowed, relief of the distending overload by venesection may be less dramatic owing to fixed anatomical obstruction, and the procedure may have little influence in increasing flow through narrowed orifices. It will be noted later that valvular heart disease also gives less favourable responses to other therapeutic agents.

The influence of venesection on pulmonary heart disease is also much less favourable.[4] It seems quite probable that in severe emphysema where the venous pressure and cardiac output are somewhat above the normal average level that the raised venous pressure may at this stage be part of the 'compensating' mechanisms maintaining the output at the high level necessary for oxygenation of the tissues (Fig. 2). Reduction of this raised venous pressure may be accompanied by a decrease in cardiac

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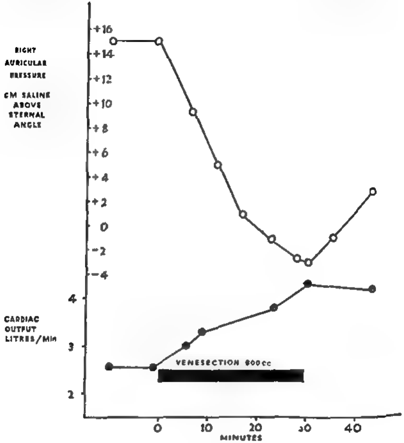

Fig. . The effect of venesection [illegible]

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Another factor, however, is involved in venesection. Although the cardiac output increases, the arterial pressure in these instances

but there is a good deal to suggest that at the peak of the diuresis the blood volume may be reduced.[29] If such reduction of blood volume does occur it may lead to a 'venesection-like' action with consequent cardiac output improvement. In this manner general clinical improvement may be initiated by mercurial diuretics by the following chain of events:

1. Increased elimination of water and salt.

2. Secondary reduction in plasma volume.

3. Reduction of venous pressure.

4. Reduction of cardiac over-distension.

5. Cardiac output improvement.

6. Increased renal blood flow.

7. Further increase in water and salt elimination and clearance of oedema from improved cardiac and renal function.

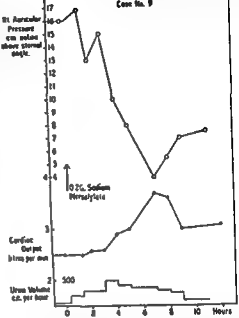

FIG. 5. The effect of sodium mersalylate on right auricular pressure and cardiac output in a case of ischaemic heart disease with aortic stenosis. Four to 7 hours after the injection the right auricular pressure fell considerably and the cardiac output had risen from 2.4 to 3.8 litres per minute. After that the right auricular pressure rose again and the cardiac output fell slightly. (Reproduced from *Clinical Science*.)

These mechanical consequences of mercurial diuresis may be partly responsible for the occasional astonishing successes resulting from mercurial diuretics, but in certain instances of cardiac failure we are all aware that mercurial diuretics spectacular at the beginning may later cease to act effectively. It is worth pondering whether in such patients the haemodynamic response to the drug may be inadequate or poor, while striking and sustained diuretic responses may be achieved in those in whom the heart

output with little benefit to the patients. It is also obvious that venesection in the presence of pericardial effusion or constrictive pericarditis is unlikely to be accompanied by any clinical improvement, but rather the reverse, as it would tend to reduce a necessarily high venous pressure.

Mercurial diuretics. The action of organic mercurials on the kidney is well established. They act on the tubule cells of the kidney where they reduce the reabsorption of water and salt from the glomerular filtrate.[26] The effect of mercurial diuretics in promoting the elimination of large volumes of urine in oedematous cardiac patients is well known. If this were the only action of mercurials their use in cardiac failure might be regarded as purely symptomatic treatment. The mere reduction of oedema fluid *per se* might not be expected to do anything to ameliorate the other circulatory disturbances which would remain unaltered underlying faults. Nevertheless, clinical experience showed that mercurial diuretics could often be used in patients with cardiac failure with very considerable general therapeutic benefit, quite apart from the reduction of discomfort caused by the oedema. Even in the absence of demonstrable peripheral oedema, mercurial diuretics were found to reduce the frequency of attacks of nocturnal dyspnoea in patients with left ventricular failure.

With these facts in mind the action of mercurial diuretics was studied by Pugh and Wyndham.[27] Cardiac catheters were in the right auricle for periods up to 10 or 12 hours in cardiac patients in order to study the circulatory reactions to diuresis. As most mercurial preparations contain added theophylline, it was necessary to give a mercurial preparation which contained none of the latter substance. It became quite clear that during a mercurial diuresis the pressure in the right heart fell, often very considerably, and with this venous pressure reduction the output of the heart tended to rise (Fig. 5). This pressure-reducing action of mercurial diuretics has also been noted by Lenègre and his colleagues.[28]

There is nothing in the pharmacological literature to suggest that mercurials have any direct stimulating action on the heart,

CHAPTER III

THEOPHYLLINE-ETHYLENE-DIAMINE

THEOPHYLLINE-ethylene-diamine, perhaps better known under its numerous trade names, has gained an established place in cardiac therapy. In common with other xanthine derivatives, it has been recognized as a diuretic having a direct action on the kidneys. This action has been studied by various renal clearance techniques, and although in the initial stages renal blood flow may be increased, the diuresis often outlasts the increased circulation rate through the kidney. There is some evidence of increased glomerular filtration, but decreased tubular reabsorption is the main mechanism involved in increasing the flow of urine.[26]

In addition to this action on the kidney, theophylline-ethylene-diamine also has an important action in abolishing Cheyne-Stokes respiration. The ethylene-diamine component of the drug apparently stimulates the medullary respiratory centre while theophylline seems to prolong this action[24] (Fig. 6).

A third action of theophylline-ethylene-diamine is on the coronary vessels, which it is said to dilate and, indeed, in the isolated heart or heart-lung preparation the coronary blood flow may be remarkably increased as a result of the action of theophylline. The drug also has a stimulating effect on the myocardium, which has often been demonstrated in the isolated heart or the animal heart *in situ*, but there has often been some doubt as to the importance of this stimulating action. Boyer claimed that this adrenaline-like stimulating action of theophylline may in fact be the primary action on the heart, with coronary vasodilatation a secondary consequence resulting from the increased metabolic needs of the myocardium.[25] Work in Carl Schmidt's department seems to confirm this view.[26]

Cheyne-Stokes breathing is particularly likely to occur in patients with severe left ventricular failure due to hypertension,

has responded well to relief of the venous distending overload.

Mercurials are an integral part of a régime of therapy in atients with congestive heart failure which has been developed y Gold and his associates[30] at Cornell. The patient is put at ed-rest or at rest in a chair. The diet consists solely of 4–6 glasses f milk daily. He receives an adequate water intake of at least quarts daily. He is digitalized and also given a daily intrauscular dose of mercuhydrin. The course is guided by body eight. When he becomes ambulant the diet is increased, but ooking salt and table salt are avoided. The interval between jections of the mercurial is lengthened, once the weight chart is shown that no further weight loss follows each mercurial jection. This outline plan is a reasonable one which is followed principle by many physicians.

The importance of salt restriction in helping to reduce oedema s been fully substantiated. It has been shown from the work Merrill[31] and others that the kidney tubules in heart failure absorb sodium more avidly than the normal kidney. A negative lt balance, i.e. loss of sodium, may be achieved (1) by merrials which increase elimination of sodium, or (2) by reducing dium intake. Under the latter circumstances the small amounts sodium eliminated by the kidney in heart failure may be ough to achieve results somewhat similar to those produced by ercurials.

There is, however, a disadvantage to the over-vigorous use of is salt-depleting régime. Salt depletion leads to serious impairent of kidney function,[32] and, especially in hypertensive and teriosclerotic patients, uraemia may be precipitated. The gime of mercurials and salt restriction, therefore, should be ed with full knowledge of its possible disadvantageous conseiences. The action of mercurials in precipitating attacks of ut should not be forgotten.[33]

THEOPHYLLINE-ETHYLENE-DIAMINE

THEOPHYLLINE-ethylene-diamine, perhaps better known under its numerous trade names, has gained an established place in cardiac therapy. In common with other xanthine derivatives, it has been recognized as a diuretic having a direct action on the kidneys. This action has been studied by various renal clearance techniques, and although in the initial stages renal blood flow may be increased, the diuresis often outlasts the increased circulation rate through the kidney. There is some evidence of increased glomerular filtration, but decreased tubular reabsorption is the main mechanism involved in increasing the flow of urine.[33]

In addition to this action on the kidney, theophylline-ethylene-diamine also has an important action in abolishing Cheyne-Stokes respiration. The ethylene-diamine component of the drug apparently stimulates the medullary respiratory centre while theophylline seems to prolong this action[34] (Fig 6).

A third action of theophylline-ethylene-diamine is on the coronary vessels, which it is said to dilate and, indeed, in the isolated heart or heart-lung preparation the coronary blood flow may be remarkably increased as a result of the action of theophylline The drug also has a stimulating effect on the myocardium, which has often been demonstrated in the isolated heart or the animal heart *in situ*, but there has often been some doubt as to the importance of this stimulating action. Boyer claimed that this adrenaline-like stimulating action of theophylline may in fact be the primary action on the heart, with coronary vasodilatation a secondary consequence resulting from the increased metabolic needs of the myocardium[35] Work in Carl Schmidt's department seems to confirm this view.[36]

Cheyne-Stokes breathing is particularly likely to occur in patients with severe left ventricular failure due to hypertension,

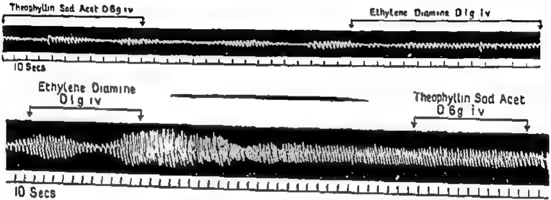

FIG 6 The effect of theophylline-ethylene-diamine on Cheyne-Stokes respiration In cases of left ventricular failure the upper record shows little immediate response from theophylline alone, while the addition of ethylene-diamine immediately *regularized the respiration* In the lower record ethylene-diamine produced tremendous stimulation of respiration with dyspnoea which settled down after about 2 minutes. Theophylline added at this time gave no further immediate response. (Reproduced from the *Lancet*)

coronary arteriosclerosis, and aortic valvular disease. In this group the immediate therapeutic effects of theophylline-

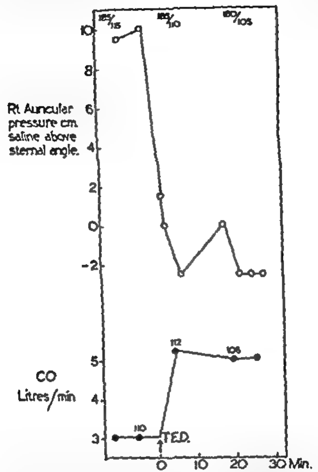

FIG. 7 The effect of theophylline-ethylene-diamine on right auricular pressure and cardiac output in hypertensive failure. 0·5 gramme theophylline-ethylene-diamine intravenously is followed within 5 minutes by a precipitate fall in right auricular pressure and the cardiac output rises steeply from a low to normal figure. This is accompanied by conspicuous symptomatic improvement.
(Reproduced from *Clinical Science*.)

ethylene-diamine can be dramatic, as a result of combined respiratory and circulatory actions. In hypertensive cardiac failure, in particular, the haemodynamic reaction to theophylline-ethylene-

diamine is rapid and striking (Fig. 7). The venous pressure falls, often within five minutes, while the cardiac output goes up steeply from low to normal figures.[37] This action seems to be entirely dependent on the theophylline part of the compound, only insignificant changes resulting from the administration of ethylene-diamine. When compared with the results of mechanical lowering of venous pressure by congesting cuffs round the thighs, the cardiac output response to theophylline-ethylene-diamine was always greater (Fig. 8). This indicates that the

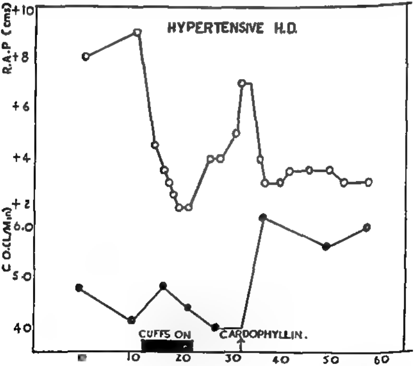

FIG. 8 Comparison of the effects of mechanical reduction of right auricular pres- [illegible]

demonstrates that direct stimulation of the myocardium is the principal mechanism involved and that primary venous pressure reduction plays little part (Reproduced from *Clinical Science*.)

cardiac output increase is due to a stimulating action of theophylline on the myocardium, and that the action is not explained by any peripheral venous pressure-reducing effect of the drug. The action of theophylline on the normal heart is also a stimulating one, but the action is transient and unless frequent measurements are taken it may easily be overlooked.

It is perhaps interesting to note that the cardiac stimulating effect of the xanthine derivatives was first suspected by Curschmann in 1873.[36] He observed violent pulsation of the heart in a young woman who had attempted to procure an abortion by drinking a decoction of half a pound of coffee.

There are several further interesting points about the circulatory action of theophylline-ethylene-diamine in cardiac failure:

1. The responses are generally better in patients with hypertensive heart failure than in patients with mitral stenosis.[37] In the latter disease it is possible that the valvular obstruction imposes a limit on the possibility of cardiac output increase as a result of cardiac stimulation.

2. Its action is transient, lasting 20–30 minutes as a rule, but the speed of action is of peculiar benefit during attacks of paroxysmal orthnopnoea due to left heart failure. Recovery from such attacks once produced may, of course, be maintained, but this is not necessarily the result of any prolonged pharmacological action of the drug.

3. Theophylline-ethylene-diamine may also produce dramatic temporary responses in the dying heart. On the day of death we have frequently encountered transient recovery of consciousness and coherence from the use of the drug, but usually within half an hour the patient slips back into a state from which no further recovery is possible. There also seem to be instances in which, when digoxin has apparently failed to produce any satisfactory response in the hour following injection, theophylline will initiate quite significant haemodynamic improvement.

Digoxin and theophylline may be given in succession with summation of their two actions (Fig. 9).

The action of theophylline-ethylene-diamine is best seen

following intravenous injection. The full dose is 0·5 gramme for an adult, but it must be injected slowly in 30–40 ml. saline. If

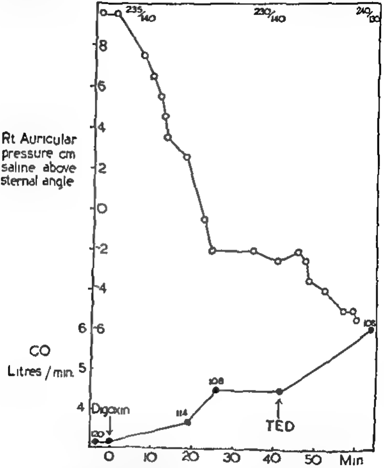

FIG 9 Summation of the actions of digoxin and theophylline-ethylene-diamine. Digoxin produced a striking fall in right auricular pressure and rise in cardiac output Further changes in a similar direction were produced by theophylline-ethylene-diamine (Reproduced from *Clinical Science*)

injected rapidly, its action on the respiratory centre is such that it precipitates hyperpnoea and perhaps dyspnoea A good technique in patients with Cheyne-Stokes respiration is to inject

a quarter of the total syringeful during the phase of apnoea over four successive cycles of the waxing and waning respiration. It will usually be found by the third injection that the phase of apnoea has been greatly shortened or has disappeared.

The increased strength of contraction of the heart after theophylline is so striking that it seems unfortunate that this action cannot be prolonged. Its action following intravenous injection tends to be transient and may often pass off within half an hour. In refractory cases of cardiac failure it may be tried by mouth in doses of 0·3 gramme thrice daily in addition to digitalis. This is probably the maximum dose which can be tolerated, and, unfortunately, even this dose is frequently the cause of much gastro-intestinal irritation, with abdominal colic and diarrhoea as troublesome symptoms which necessitate cessation of administration. A recent suggestion to overcome this difficulty is injection of the diluted drug through a fine catheter which the patient may be taught to pass into his own rectum. The writer, however, has no experience of this method.

In view of the stimulating action of theophylline on the heart it is well to sound a note of warning on its use as a coronary vasodilator Boyer is probably correct when he states that the increased coronary flow is a secondary consequence of myocardial stimulation Efforts to show that the drug modifies the myocardial degeneration following ligation of the coronary arteries have not been very successful[39] Merrill[40] records the induction of cardiac pain and sudden death after the injection of aminophyllin in coronary thrombosis, and the stimulating action of the drug may well add to such risks.

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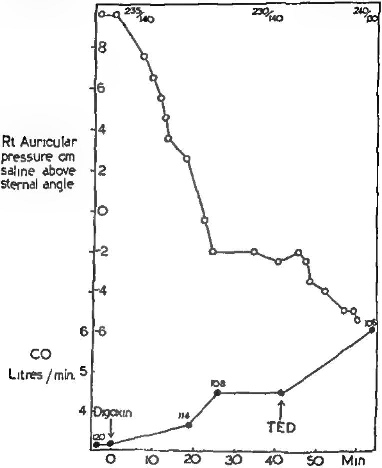

injected rapidly, its action on the respiratory centre is such that it precipitates hyperpnoea and perhaps dyspnoea A good technique in patients with Cheyne-Stokes respiration is to inject

of the problem in human heart failure by means of cardiac catheterization was urgently needed.

1. *The significance and validity of cardiac output and intra-cardiac pressure measurements.* It is necessary at this point to state quite clearly the significance of some of the quantitative measurements which may be obtained by cardiac catheterization. It is now realized that some of the earlier results obtained by ourselves and others may not have been outside the limits of experimental error. An intra-cardiac catheter does not invariably yield a completely mixed sample of returning venous blood. Blood from the coronary sinus flowing into the right auricle has a more reduced oxygen content than mixed venous blood, and a catheter lying near the coronary sinus may give a sample which is quite misleading. It was stated some time ago[17] that about one sample in twenty might differ so grossly in oxygen content from a sample taken immediately before that it could clearly not be used for cardiac output calculation. It is necessary (*a*) to leave the catheter unchanged in position once a favourable position has been reached: for reliable samples the right ventricle is better than the right auricle, and the best position is probably the pulmonary artery; (*b*) to take duplicate samples or samples in close succession at all critical points of an experimental observation. Close agreement of paired samples or an even upward or downward trend of output increase the value of the estimations. With these precautions, critical analysis of paired successive samples analysed in a Haldane apparatus for the oxygen unsaturation has yielded the following estimates of possible error:[48]

Coefficient of variation of paired samples for oxygen unsaturation	$= \pm 3{\cdot}5\%$
Coefficient of variation of oxygen uptake by spirometry from measurements before and after the usual experimental period of one hour	$= \pm 5\%$

By adding the variances ($3{\cdot}5^2 + 5^2$) and taking the square root, the coefficient of variation of a single output estimation is $\pm$ 6 per cent Where single estimations only are made a difference

CHAPTER IV

DIGITALIS AND STROPHANTHUS

THE conditions under which digitalis bodies exercise a favourable influence in heart failure still remain very mysterious and ill understood. Clinicians have been aware for decades that its beneficial action, while sometimes dramatic and striking, has on other occasions been apparently completely lacking. A succession of opinions has been forthcoming to try to account for the apparent discrepancies and unpredictability of action. Mackenzie held that therapeutic benefit was largely determined by its slowing action on the heart, and that its effect was therefore most pronounced in cases of auricular fibrillation.[41] Mackenzie's pupil, Lewis,[42] sustained this idea until near the end of his life. There was, nevertheless, adequate evidence from clinical studies that digitalis could produce quite striking benefit in patients with sinus rhythm in whom the slowing action was less prominent and sometimes insignificant.[43, 44] There was adequate pharmacological support for a stimulating action of digitalis bodies on the myocardium, particularly when the heart had failed under certain experimental conditions.[45, 46] These experimental conditions included (*a*) spontaneous weakening after a time of the isolated heart or strips of papillary muscle suspended in saline, (*b*) heart failure induced by the action of large doses of camphor, chloral and similar substances. There was, however, no justification for assuming that the forms of heart failure seen clinically reproduced a metabolic and functional state of the myocardium comparable to that produced in the pharmacological laboratory The unpredictability of action of digitalis bodies in clinical heart failure certainly rendered it quite certain that the stimulating action was often either absent or too slight and transient to be obvious. Further direct investigation

of choice and Hamilton manometers,[49] condenser manometers (Hanssen),[50] or strain gauges[51] may be used. Very exact contour records are difficult to record at the outer end of a long catheter, but close approximations to the systolic and diastolic pressures are obtained.

If we take a level 5 cm. behind the sternal angle as the mid-point between the anterior apex of the heart and its posterior border,[49] the intra-ventricular diastolic pressure at the end of diastole fluctuates closely round this zero level in supine normals, while the systolic pressure ranges from 15–30 mm. Hg. above this point. In barrel-chested individuals the mid-part of the heart may lie considerably lower than this arbitrary point, and this has to be taken into account in considering pressures in emphysema.

The optical records of right ventricular pressure are of great interest in heart failure. Diastolic pressure within the ventricle is usually raised in parallel with pressures within the right auricle.[49] In fact, diastolic pressures within the ventricle are only slightly below the pressures within the auricle during the period of ventricular filling (Fig. 10). Cournand claims that the

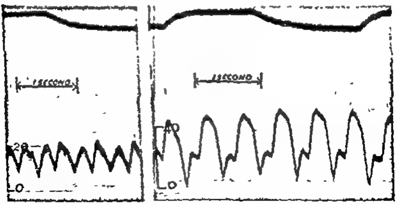

FIG 10. Constrictive pericarditis Left hand tracing shows the pressures within the auricle The higher peaks represent auricular systole It will be noted that the pressures reached correspond almost exactly with the peaks of pressure recorded from the ventricle in diastole. The sensitivity of the manometer has been reduced while taking the ventricular pressure record

of 12 per cent (twice the standard error) must be insisted on for significance.

In patients with heart failure consequent on bronchitis and emphysema, owing to inconstancy of lung ventilation, the arterial oxygen saturation undergoes quite considerable fluctuations which have not yet been statistically analysed, but it is well to remember that single cardiac output determinations in this condition are probably not significant unless they differ by at least 20 per cent. These figures apply to *single* estimations of cardiac output. When more numerous right heart samples are taken, of course, the significance of smaller differences may be established, but the coefficient of variation cannot be reduced under 5 per cent without repeated estimations of oxygen uptake. Consistent changes in one direction following some test procedure in a series of samples may help to establish the validity of small changes in output.

Intra-cardiac pressure measurements. Right atrial pressure may be measured as a mean value with a water manometer. To be satisfied with the readings, respiratory fluctuations should be present and the catheter used should allow a free flow and fairly rapid settlement of the manometer to a stable level. The catheter should be flushed between readings. With the patient in a steady resting state, spontaneous fluctuations of more than 1 cm. are unusual. If a cardiac patient is restless, however, considerable fluctuations are possible, and observations made during a disturbed period must usually be discarded Quietness and a steady base line are necessary before valid observations are obtained: under such conditions a rise or fall of 2 cm. water is probably significant.

Right ventricular pressure may be measured as a mean value. Pulsations are more vigorous in the manometer and special care must again be taken to ensure that pulsations are 'free'. Should the catheter tip within the heart have its opening temporarily blocked by contact with the heart wall during contraction, the peak of intra-ventricular pressure will not contribute to the 'mean' pressure and a false low reading will be obtained

Optical recording of right ventricular pressure is the method

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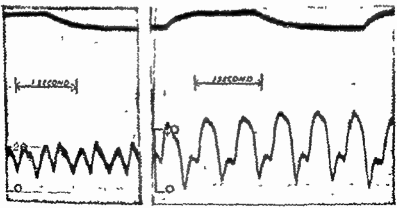

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end-diastolic pressure in the ventricle parallels the mean right auricular pressure, and in the great majority of cases this is true: an obvious exception is tricuspid valve incompetence.

Systolic pressure within the right ventricle corresponds to systolic pressure in the pulmonary artery[19] (Fig. 11) The pulmonary artery pressure is nearly always raised in cardiac failure (Fig. 12). It rises either as a consequence of vascular obstruction in the lungs in pulmonary heart disease, or as a result of raised pulmonary venous pressure from the left ventricle or auricle, for example, in hypertensive disease or mitral stenosis. There are only rare exceptions to the rule that the pulmonary arterial pressure is raised in heart failure.

The rise in pulmonary arterial pressure may be very considerable during attacks of dyspnoea due to left ventricular failure[22] We have seen such systolic pressures rise to over 80 mm. mercury. When patients on the verge of left heart failure make any muscular effort the pressure in the pulmonary artery rises in contrast with normals in whom mild exercise is accompanied by an increase in cardiac output without increase in pulmonary arterial pressure.[22,23] Rest, as might be expected, brings down the pressure in the right heart in patients with left ventricular failure. Dyspnoea and any state of alarm may cause the pulmonary artery pressure to rise in such patients. Again we should emphasize the necessity of making all base-line observations under conditions of rest, ease, and comfort for the patients, and only judging the effects of drugs or other procedures after a satisfactory steady state is reached

Before going on to discuss the reactions of the human heart to digitalis bodies it should be emphasized that the situation is most complex for various reasons. Digitalis has a number of actions on the heart and circulation, but from the haemodynamic standpoint we need only consider the following.

(*a*) it stimulates stronger contractions in certain types of failing myocardium;

(*b*) it slows the ventricle by vagus action or by producing partial heart-block especially in auricular fibrillation,

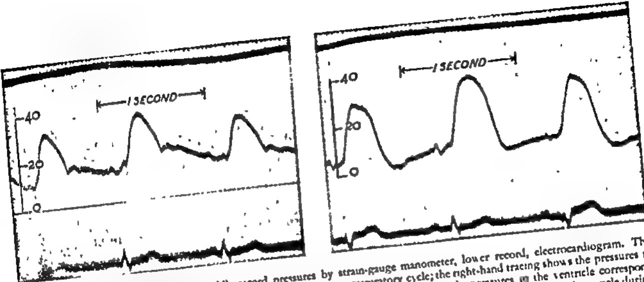

FIG 11 Upper record respiration, middle record pressures by strain-gauge manometer, lower record, electrocardiogram. The left-hand tracing shows the pressure in the pulmonary artery during a respiratory cycle; the right-hand tracing shows the pressures in the right ventricle a few seconds later under identical conditions Note that the peak systolic pressures in the ventricle correspond exactly with those in the pulmonary artery Pressures in the right ventricle during diastole correspond to those in the auricle during the same period The end diastolic pressure immediately before contraction of the ventricle is taken as the ventricular filling pressure.

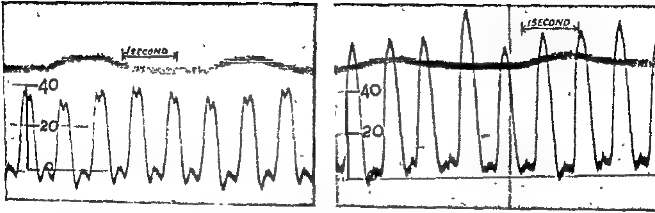

FIG 12 Early hypertensive heart failure The pressure record on the left shows the control pressures in the right ventricle. Twenty-seven minutes after 1·5 mg digoxin the arterial pressure had risen and the patient had developed an attack of left ventricular failure with orthopnoea, pulmonary congestion. The systolic pressure in the right ventricle had risen from 37 to 68 mm. Hg. while the end-diastolic pressure had also risen This represents an induced attack of left ventricular failure The cardiac output fell slightly

(*c*) it induces ectopic rhythms;

(*d*) it raises arterial pressure;

(*e*) it may reduce venous pressure independently of cardiac output change.

Any one of these actions may occur independently of the others: any one of them may fail to occur in certain circumstances (Table). Responses may vary according to the etiological variety of heart disease, and according to the stage of the disease. This is one reason for the difficulties which have arisen in interpretation of results and the confusing divergencies of opinion as to what constitutes a typical response

2 *The stimulating action of digitalis on the failing myocardium.* It is widely agreed that digitalis bodies have little measurable effect on contractility of the normal myocardium.[6, 52, 54] The output of the heart in normal animals tends to fall, and in man the action of digoxin or ouabain in normal subjects is usually to produce no change in cardiac output although on some occasions there is a slight fall in the venous pressure with a fall in cardiac output. Although there has been a good deal of evidence in the literature that digitalis produces a slight venous pressure fall in normal animals[55] and man,[56] this occurrence is now recognized as being much less constant than was originally thought. The venous pressure reduction which takes place is often small, 2–3 cm. of saline at most. Such changes of pressure, however, may represent changes in diastolic tension within the ventricles of some physiological significance if we accept Wiggers' interpretation of Starling's Law of the Heart. However, the doubts cast on the simple applicability of Starling's Law to the normal human heart *in situ* in recent years has now made it difficult to accept without reserve the simple explanation which seemed likely some years ago that cardiac output and venous pressure fall in parallel as the result of digitalis action in normal man. We can go no further at the present day than to say that digitalis has no stimulating action measurable by output estimations in the normal heart, but that sometimes venous pressure and cardiac output may fall in parallel

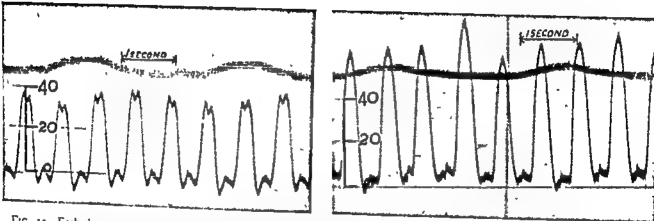

FIG. 12. Early hypertensive heart failure. The pressure record on the left shows the control pressures in the right ventricle. Twenty-seven minutes after 1·5 mg. digoxin the arterial pressure had risen and the patient had developed an attack of left ventricular failure with orthopnoea, pulmonary congestion. The systolic pressure in the right ventricle had risen from 37 to 68 mm. Hg. while the end-diastolic pressure had also risen. This represents an induced attack of left ventricular failure. The cardiac output fell slightly

When a favourable response to intravenous digoxin or lanatoside C is achieved in patients with heart failure, the injection is followed within 20–30 minutes as a rule by a fall in right atrial pressure, accompanied *later* by a distinct and significant rise in cardiac output[5, 21] (Fig. 13). This action has been demonstrated repeatedly, and it seems to be the most constant immediate response ushering in the clinical improvement so often seen following digitalization.

The manner in which these changes are brought about was the subject of some initial perplexity. It was found, for example, that comparable increases in cardiac output might be induced by similar reductions in venous pressure produced mechanically by venesection or by congesting cuffs round the thighs[22] (Fig. 14). This opened up once again the possibility, suspected previously by Dock and Tainter, Katz and others, that a primary venous pressure-reducing action of digitalis might be of importance and that cardiac output increase might be secondary to this. When more detailed comparisons were made, however, there was a difference. Cardiac work after digoxin was greater than that after venesection (Fig. 15). As mentioned above, venesection is often accompanied by lowering of arterial blood pressure while digitalization may even raise the arterial pressure. When this factor of blood-pressure change is taken into account in calculating the work of the left ventricle, it is clear that the work of the heart is greater after digoxin than after venesection.[23] About the time we reported these findings, further work was done with ouabain by Bloomfield, Ellis, and others,[57] showing that in various types of heart failure this substance could increase the cardiac output without any accompanying venous pressure reduction. A stimulating action of ouabain was thus established which was quite independent of any effects on venous pressure (Figs. 16 and 17) This work with ouabain, which has been confirmed,[54] made it highly probable that the differences in cardiac work after venesection and digoxin were in fact due to a direct stimulating action of digoxin on the failing human myocardium. Following further work in our own school we have also become aware of

TABLE

EXAMPLES [illegible] CONDITIONS IN WHICH THE VARIOUS ACTIONS OF DIGITALIS MAY OR MAY NOT BE EXPECTED TO OCCUR

Action	*Often present in*	*Often absent or ineffective in*
Stimulation of contraction	Hypertensive heart failure	Normal hearts
Slowing of ventricle in auricular fibrillation	Hypertensive heart failure Mitral stenosis	Thyrotoxicosis Pulmonary embolism Auricular fibrillation without failure
Ectopic beats	Severe myocardial disease and advanced failure	Early heart failure
Arterial pressure rise	Following *full* intravenous dosage	Oral administration [illegible] sub-maximal intravenous dosage
Venous pressure reduction	Hypertensive heart disease Ischaemic heart disease	During induced rise in arterial pressure Normal hearts Anaemic heart failure

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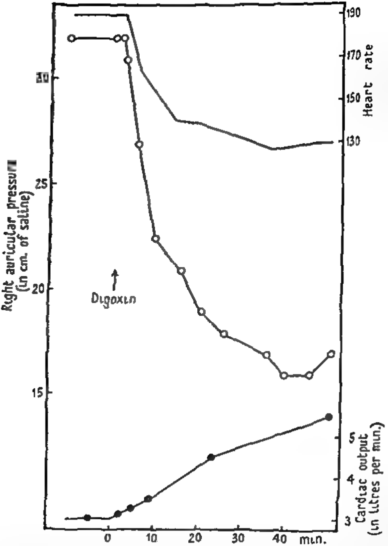
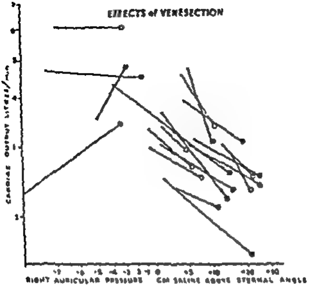


FIG. 13. Severe congestive failure with auricular fibrillation and rapid ventricular rate in thyrotoxicosis 1 5 mg digoxin produced a rapid fall in right auricular pressure, a rise in cardiac output, and a considerable reduction in ventricular rate. *Note the early fall in* R A P preceding significant cardiac output change (Reproduced from *Quarterly Journal of Medicine*)



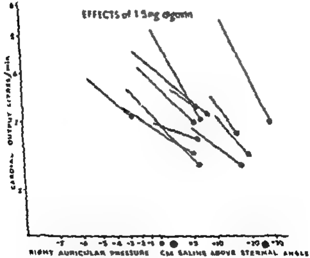


FIG. 14 Comparison of the effects of venesection and digoxin in patients with low output heart failure drawn on similar logarithmic scales The dot marks the initial reading and lines are drawn to the final readings. The open circles in the

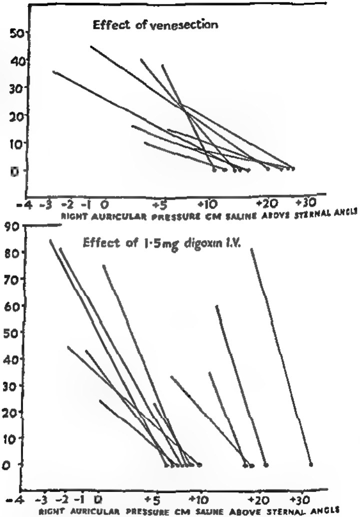


FIG 15. Comparison of venesection and digoxin on the work of the left ventricle Work is calculated by multiplying cardiac output by mean arterial pressure Venesection produces a 10–40 per cent increase in work while digoxin produces a 20–80 per cent increase in work (Reproduced from *Clinical Science*)

numerous instances in which intravenous digoxin produces no fall in venous pressure and no change in cardiac output during

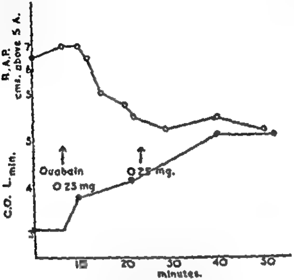


Fig. 16 The response to ouabain in hypertensive heart disease. Following 0·24 mg ouabain the cardiac output undergoes an immediate rise which *precedes* right auricular pressure fall. At the end of 20 minutes a further 0·25 mg is followed by a further rise in cardiac output without any significant venous pressure fall. (Reproduced from *Clinical Science*.)

the period of observation; anaemic heart failure is an example.[58] Cournand and his associates have also shown that, in selected instances of left ventricular failure, the output of the heart may be increased without any significant change in end diastolic tension in the right ventricle, and therefore no change in the venous filling pressure.[59]

This accumulation of new evidence has established beyond doubt myocardial stimulation by digitalis in certain types of failing human heart, and this action may occasionally be independent of systemic venous pressure reduction. The proof of this direct myocardial action was more easily forthcoming with ouabain than with digoxin itself. This raises the possibility once more that the old claim made by Vaquez[60] and by Fraenkel[61] that

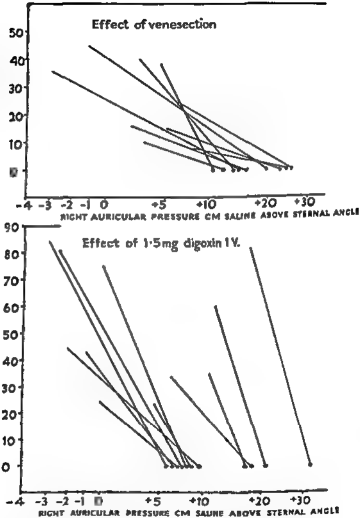
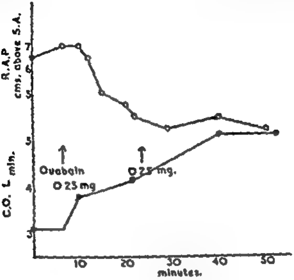


FIG. 15. Comparison of venesection and digoxin on the work of the left ventricle. Work is calculated by multiplying cardiac output by mean arterial pressure Venesection produces a 10–40 per cent increase in work while digoxin produces a 20–80 per cent increase in work. (Reproduced from *Clinical Science*.)

numerous instances in which intravenous digoxin produces no fall in venous pressure and no change in cardiac output during



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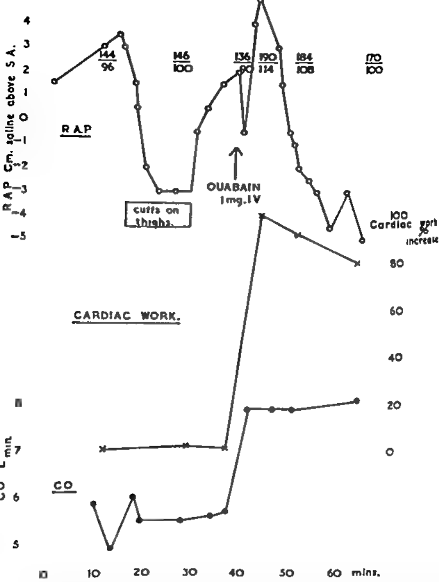


FIG 17 Comparison of venous-pressure reduction with ouabain in a case of hypertensive heart disease Reduction of venous filling pressure by mechanical means (cuffs on thighs) had no significant influence on cardiac output One mg ouabain intra-venously raised the cardiac output considerably at a similar level of venous pressure (Compare that seen at 30–60 minutes.) An immediate con-

action of ouabain

strophanthus had a stronger myocardial stimulating action than digitalis may be worthy of reconsideration. The timing of the responses to intravenous injections of digoxin and lanatoside C on the one hand and of ouabain on the other is certainly different. The first response to digoxin is a fall in right heart pressure before any measurable rise in output, while the early response to ouabain is a rise in cardiac output[44] (Fig. 18) and right ventricular pulse pressure.[57] The digitalis derivatives usually take 20–40 minutes or longer to bring about a recognizable action, while ouabain effects come on in about 5–15 minutes. The speed of action of ouabain may be quite dramatic and the drug can cause rapid disappearance of such features as pulsus alternans and triple rhythm: the rapid onset of action may have something to do with different solubilities of the two drugs, ouabain being water-soluble and digoxin alcohol-soluble. The older literature contained little satisfactory work on the comparative action of digitalis and strophanthus derivatives: there was a certain inclination to illustrate the myocardial stimulating action of digitalis bodies by strophanthin and ouabain experiments. Although some recent experiments by Loubatières [42] tend to show that while digitaline *restores the tone (diastolic tension)* of strips of failing papillary muscle, it does not have as strong an action as ouabain in increasing the magnitude of systolic contractions. Only a few experiments are illustrated however, and the work of Cattell and Gold,[16] Walker, Lourie and Burn, [61] and Walton, Leary and Jones[62] appears to indicate little quantitative difference in the action of the various glycosides.

3. *Reduction of venous pressure in the absence of cardiac output change, and other right heart pressure responses.* It was often noted that digoxin might reduce the venous pressure in certain patients with cardiac failure without any increase in cardiac output during the period of observation [5, 25, 54]. Even when cardiac output did increase it was often observed that a conspicuous venous pressure fall preceded any statistically significant cardiac output change.[54] At first these observations seemed to lend support to the idea that

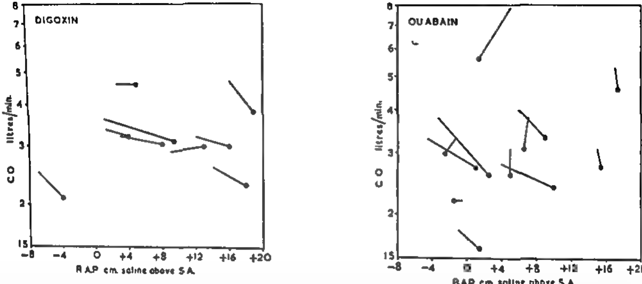


FIG 18 Comparison of the earliest responses to digoxin and ouabain in a series of patients with hypertensive heart disease. The earliest response to digoxin on the left is seen to be a fall in right auricular pressure without any significant increase in cardiac output. The earliest response to ouabain, on the other hand, is usually a rise in cardiac output without much fall in venous pressure. (Reproduced from *Clinical Science*)

venous pressure reduction was independent of cardiac output improvement and might be an important primary action of digitalis.[3] Since *primary* venous pressure reduction can no longer be invoked to explain the variety of cardiac output responses to digitalis, it is necessary to account for venous pressure reduction in the absence of cardiac output increase in some other way.

In a recent study of right ventricular pressures in patients with hypertensive and ischaemic heart disease,[43] in one third of the cases we have observed the right ventricular pressure to fall significantly in the absence of a measurable increase in cardiac output; the fall in pressure in these patients affected the right ventricular systolic pressure considerably while the diastolic pressure fell by 2–6 mm. mercury. The latter represents quite an important change in diastolic filling pressure of the right ventricle, while the much greater fall in systolic right ventricular pressure represents a great reduction in pulmonary arterial pressure This relief of pulmonary vascular engorgement was accompanied by subjective relief of dyspnoea. The fall in diastolic filling pressure of the right ventricle was paralleled by a fall in central venous pressure.

These observations are illustrated in Figs. 19 and 20. They give more detail to the haemodynamic picture than we possessed before. The pulmonary vascular engorgement (rise in systolic right ventricular pressure) exceeded considerably the degree of systemic venous engorgement (end-diastolic pressure in the right ventricle), i.e. the patients had left ventricular failure. If a patient were to develop left ventricular failure *suddenly*, his heart would fail to empty properly, and the residual blood remaining after the weak contraction would be added to the incoming blood from the still normally functioning right ventricle The left ventricle would become more distended with each beat until it was sufficiently stretched to fall into step with the right ventricle again and the stroke outputs would become equalized This would occur in a few beats and at the expense of a stepwise increase in pulmonary vascular pressures, venous, capillary, and arterial We can explain the action of digoxin illus-

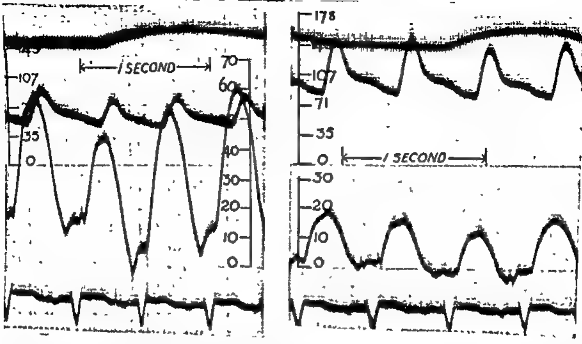
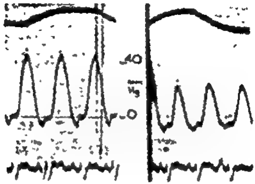


FIG 19 The response of a dying heart to digoxin The patient was a known hypertensive who had passed into severe heart failure with terminal fall in arterial pressure He remained unconscious through the observations and died 24 hours later Records from above down - respiration, arterial pressure, right ventricular pressure, electrocardiogram (recorded upside down) control observations on the left Note the high pressure in the right ventricle in systole and diastole and the low arterial pressure Thirty minutes after 1 5 mg digoxin the arterial pressure had risen and the right ventricular pressure was restored to normal Cardiac output remained unchanged at 4 litres per minute. While right ventricular pulse pressure diminished left ventricular pulse pressure must have increased

trated in Figs. 19 and 20 as a reversal of this process. Digoxin may act on the failing left ventricle, causing it to expel slightly more



	CONTROL	AFTER DIGOXIN
CARDIAC OUTPUT	3.7 L/min	3.4
R.V.P.s	43 mm.Hg	26
end d.	0.5 mm.Hg	−2

FIG. 20 Hypertensive cardiac failure From above down—respiration, right ventricular pressure, electrocardiogram Pulmonary congestion before treatment is indicated by the high right ventricular systolic pressure (43 mm Hg) This pressure, with the end-diastolic pressure, fell significantly half an hour after 1.5 mg digoxin. Cardiac output remained unchanged or possibly fell slightly

blood than the right, *but only for a few beats* until the pulmonary venous pressure has fallen, when the two sides of the heart once more fall into step The Fick method is incapable of detecting such a temporary inequality of output of the two sides of the heart, and we only observe the end result—output unaltered but pulmonary vascular pressures reduced.

In this action the normal right heart shows no response to digoxin and is, in fact, behaving in a completely physiological

fashion. When left heart failure develops with a secondary rise in pulmonary vascular pressures, the right heart is put slightly

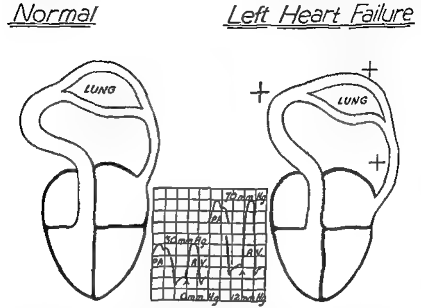


FIG 21 Diagrammatic representation of normal pressures in the right ventricle and pulmonary artery in normals and in left heart failure. The high pressure in the pulmonary artery is probably determined by high pressure in the pulmonary veins Digoxin restores this state of affairs towards the normal

under strain and the venous filling pressure rises to meet the demands. With relief of pulmonary hypertension, the diastolic filling pressure of the right ventricle falls, and with it the central venous pressure comes down a few centimetres of water (Fig. 21).

Inequality of action of digitalis on the two ventricles, with differential stimulation of the left ventricle, may thus account for some of the anomalous and puzzling responses which previously led us to make a tentative suggestion that venous pressure changes after digoxin might be primary. Reduction of pulmonary vascular pressures may well be due to shifting of blood from the lungs by increased cardiac output as suggested by Cournand and his collaborators. But the cardiac output increase is not necessarily

either sustained or measurable; it may only last a few beats. Werkö and his colleagues have recently shown that even when the output of the failing left heart does go up, as an immediate response to lanatoside C, the pulmonary blood volume is not measurably altered.[44] Perhaps reductions in pulmonary vascular tone are involved. Alternatively, it would appear that a very small volume reduction in the lung vascular bed may be accompanied by a considerable fall in pulmonary vascular pressure. Volume-pressure relationships in the lung vasculature require more detailed study before the sequence of effects after digoxin can be properly evaluated.

While the series of events illustrated in Figs. 20 and 21 is taken as a common reaction in left heart failure, there are other patterns of behaviour of right heart pressures and cardiac output.[53]

(*a*) Observations in Cournand's laboratory[49] have shown a few instances of left heart failure in which the output of the heart rises with a fall of pressure in the pulmonary vessels, but with *no change* in right ventricular end-diastolic pressure. In our experience this type of pressure reaction is unusual.

(*b*) In valvular heart disease and some cases of chronic cor pulmonale the reactions are complicated by an obstructive element and an increase in right ventricular pulse pressure follows digoxin. This is similar to the reaction to ouabain described by Bloomfield and his colleagues.[57] In a mixed series of cases with valvular disease forming the majority, Lagerlof and Werko also emphasize this type of reaction after lanatoside C.[41a] We also see this reaction sometimes after digoxin[53] The increased pulse pressure may be indicative of stimulation of the right ventricle. Fig. 19 shows how a failing left ventricle may respond in a similar way with an increase in pulse pressure but without change in cardiac output.

(*c*) Occasionally a full intravenous dose of digoxin is followed by a temporary rise in arterial pressure which precipitates further left ventricular failure with rises in both systolic and diastolic pressure in the right ventricle (Fig. 12).

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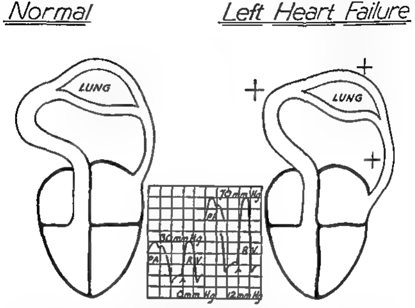

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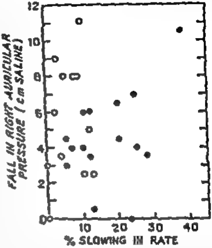


FIG. 23 Comparison of the influence of slowing of the ventricular rate on reduction of right auricular pressure in patients with sinus rhythm (circles) and auricular fibrillation (dots) While greater slowing is achieved there is no difference in the degree of venous pressure reduction and auricular fibrillation. (Reproduced from the *Lancet*)

This reaction of the arterial pressure is important for various reasons. It occurs early, coming on within 3–8 minutes, and when present it may overwhelm some of the other actions of digitalis. It may even precipitate a temporary exacerbation of breathlessness with a rise in both the venous pressure and pulmonary vascular pressures. We have seen attacks of left ventricular failure which undoubtedly followed the injection of digoxin or ouabain in full doses, and which completely overshadowed the other more beneficial pharmacological action of the drugs (Fig 12) The blood-pressure raising action, however, is likely to be transient, and it may pass off completely in 15–30 minutes, when the fall in

4. *Heart rate reduction and cardiac output change.* The old idea that clinical responses to digitalis were determined by slowing of a rapid heart has been subjected to further analysis by Kelly and Bayliss.[65] Reduction of venous congestion and improvement of cardiac output are quite as frequent and striking in patients with sinus rhythm as in those with auricular fibrillation in whom a greater reduction of ventricular rate is achieved (Figs. 22 and 23). The widespread clinical impression that results are better in patients who have auricular fibrillation may depend on the fact that pulse rate reduction by digitalis in the presence of fibrillation affords a simple guide to optimum dosage. The patient who is in heart failure with sinus rhythm offers no such easy objective guide to dosage and may fluctuate between under-dosage and toxic effects from over-dosage. This may lead to the impression that the drug is of less clinical value in such patients. In the *early* stages of digitalis action the ventricular rate reduction in auricular fibrillation seems to be vagus in origin as it can always be completely abolished by atropine in a full intravenous dose (1–2 mg.). This is in keeping with the observations of Porter[66] and also of Gold and his associates[67] that the direct action on the bundle of His develops later in the course of digitalization.

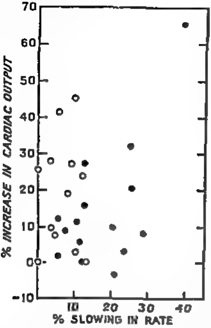
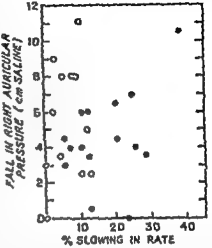


FIG. 22. Comparison of the influence of slowing of the ventricular rate on cardiac output in patients with sinus rhythm (circles) and auricular fibrillation (dots). A greater degree of slowing is achieved in auricular fibrillation, but the influence on cardiac output is similar in the two groups. (Reproduced from the *Lancet*.)

5. *Blood-pressure raising action.* It has long been known that

in experimental animals full doses of digitalis bodies raise the arterial pressure.[48] Whether such an action was demonstrable in man or not was for some time disputed. Using modern preparations, however, there is no doubt that full doses of digoxin and of ouabain are often followed by a significant rise of arterial pressure (see Fig. 19). This rise of arterial pressure may or may not be accompanied by an increase in cardiac output[54] and on analysis, therefore, it may or may not mean some increase in peripheral resistance according to circumstances. Carotid sinus regulation of blood pressure seems to be disturbed by digitalis[55] With doses below the maximal therapeutic injection dose (1·5 mg. digoxin, 1·6 mg. lanatoside C, 0·75 mg. ouabain), this blood-pressure raising response is less likely to occur



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peripheral venous pressure and rise in cardiac output may become apparent (Fig. 17). The rise in arterial pressure, particularly following the injection of ouabain, may be accompanied by curious sensations in the head. Patients describe the sensation of bursting or of some curious intolerable feeling, but once again this may be transient. In one instance, however, in a patient with cardiac failure and some accompanying mental confusion, ouabain administration was followed by increased severity of the confusional symptoms, increased restlessness, and garrulousness. It has been suggested that ouabain has some cerebral vasoconstrictor action.

6. *The production of ectopic beats.* This well-known property of digitalis constitutes one of the possible risks which must be taken when the drug is used in the therapy of severe heart failure. There can be few physicians who have not experienced the sudden demise of a cardiac patient within half an hour of digitalization, particularly with massive dosage. Three such instances have occurred in patients under the writer's care in the last 10 years. In two the condition was recognized as ventricular tachycardia. The second and more common complication is the development of pulsus bigeminus. The latter condition is especially liable to develop in the later stages of mitral stenosis and in patients with some form of severe myocardial disease. It seems that pulsus bigeminus has never been induced by digitalis dosage in previously normal animal hearts.[70] Pulsus bigeminus, therefore, is probably the combined effect of digitalis and severe myocardial disease. Once it occurs the physician is in a dilemma. Continuation of digitalis may be followed by death, and withdrawal of the drug usually marks the end of any possibility of benefit from this particular remedy. The irregularity may persist for weeks after digitalis has been withdrawn, and on attempting to restart digitalis even with very small dosage, bigeminy is likely to recur. Bigeminal rhythm may, of course, occur in certain patients with severe myocardial disease independently of digitalis administration, and in its presence it can never be wise to give digitalis. Bigeminy, therefore, condemns the patient to treatment by

remedies other than digitalis and it usually marks the final stage of myocardial breakdown when digitalis has ceased to be of benefit.

7. *Speed of action: cumulation.* Much of the new information on the responses of the failing human heart to drugs has been obtained during spells of observation lasting approximately one hour and on occasions longer. Active preparations of digoxin are usually followed by a venous pressure fall which is manifest within 20 minutes and is followed later by a rise in cardiac output. Definite responses of cardiac output and venous pressure are present in half to three-quarters of an hour. Lanatoside C, according to Stead,[23] appears to act in a similar time period, and the earliest manifestation is also a fall in right atrial pressure. Ouabain, on the other hand, acts much more rapidly. Its effects may be seen within five minutes in many instances and the cardiac output rise may be the first manifest response. Digitaline, used by Lenègre and his colleagues, appears to act in half to one hour.[71] While quite remarkable and definite improvements in cardiac output and relief of venous congestion may be demonstrable within an hour, it is not yet established that these reactions represent the full and complete therapeutic responses. Other methods of observing cardiac output over periods of days may on occasions demonstrate clinical improvement with measurable increases in output and further diminution of congestion of a degree beyond those produced by intravenous digoxin within the hour.[72] A great deal of work will have to be done to establish the part played by digitalization in these later ameliorations. Once the vicious circle of cardiac failure has been successfully broken by intravenous injection of digitalis preparations, bed rest alone may contribute much to the completion of the cure.

The well-known tendency of digitalis to be cumulative is a troublesome bugbear to the physician, particularly when he is dealing with a cardiac breakdown in a patient who is already receiving the drug. It is possible that too much attention to this may inhibit effective treatment. Ray and La Due[73] have shown that it is quite possible to achieve gratifying therapeutic results by

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The length of this section is a revelation of our fundamental ignorance of the mode of digitalis action. Our knowledge of the way in which this important substance works is still empirical. More knowledge of the mechanisms of muscular contraction and their breakdown in fatigue will be needed before we can see the issues clearly. Visscher[74] was of the opinion that the heart worked with greater efficiency after digitalis, i.e a greater proportion of its metabolism appeared as external work. Katz,[75] on the other hand, claims that the heart does more work and that change in efficiency is less important. Finkelstein[76] has recently shown an increased oxygen usage by the heart under digitalis An excellent review of the metabolic action of the cardiac glycosides has been published by Wollenberger [76a]

Stewart and Cohn[77] showed that successful digitalization reduced the size of the heart. Reduction in size may sometimes be very rapid and striking. Whether this represents a change in 'tone' is debatable. It may equally be a secondary result of recovery from heart failure in other ways, with disappearance of the overloading, overstretching influence of the high filling pressure.

There remain multitudes of problems to be solved in relation to digitalis action Their study in intact man will continue to be profitable, for in the course of such investigations we shall continue to learn more about the fundamentals of heart failure, and the significance of the variety of its clinical manifestations.

CHAPTER V

SPECIAL THERAPEUTIC PROBLEMS

TO regard digitalis as a panacea to be pushed in all forms of cardiac embarrassment is just as irrational as to recommend liver therapy in all forms of anaemia. Success is only likely to be obtained in certain types of patient, and between those who make a dramatic clinical response and those in whom the drug fails to act utterly lies an ill-defined group of patients where digitalization still remains a therapeutic trial, where success sometimes is achieved but may equally frequently be absent. The reason why digitalis sometimes works and sometimes fails still seems to be unknown. It is difficult to enunciate any sure guiding principles, but the following statements seem to be generally true:

1. Digitalis is likely to increase cardiac output in the low output type of failure, i.e. failure accompanying hypertensive, ischaemic, and valvular heart disease.

2. The responses are better and more dramatic in the early attacks of failure than in the later stages where the heart seems to have lost its ability to produce or maintain a response.

3. In high output types of congestive failure (emphysema, anaemia, arteriovenous aneurysms) digitalis is much less likely to be accompanied by significant clinical improvement.

Hypertensive heart disease. In the early stages hypertensive heart failure may be manifested by attacks of nocturnal dyspnoea and slight breathlessness on effort At this stage considerable benefit results from digitalis administration. Later, when failure is sufficiently severe to demand bed rest, digitalis still continues to yield worthwhile results. These patients can often be dramatically relieved and have periods of relative well-being, but with the inexorable progress of the disease intervals become shorter and attacks of failure more intractable at each successive hospital admission

giving additional doses of digitalis to patients who, in their view, have passed into failure because they were not receiving enough. In such patients *one must proceed with caution* and use small doses of more rapidly eliminated preparations such as strophanthin and ouabain. Ray and La Due hold that even electrocardiographic evidences of digitalis effects need not contraindicate further digitalis administration.

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There remain multitudes of problems to be solved in relation to digitalis action. Their study in intact man will continue to be profitable, for in the course of such investigations we shall continue to learn more about the fundamentals of heart failure, and the significance of the variety of its clinical manifestations.

digitalis either reduced the venous pressure or raised the cardiac output, or both.

Cor pulmonale. Heart failure of pulmonary origin is proving to be an extremely complex affair.[4, 75] Cases can be broadly subdivided into (*a*) obstructive and (*b*) asphyxial varieties. In the former the cause of the failure lies in some form of obstructive vascular disease in the lungs which may result from primary pulmonary hypertension, recurrent pulmonary embolism, embolic carcinomatosis, pulmonary bilharziasis, and the like. The asphyxial or anoxic varieties result from bronchitis and emphysema, and also in the course of other diseases interfering with air entry to the lungs, such as peribronchial carcinoma due to lymphatic spread of tumour into the lung tissue, the primary site of such growth usually being in the abdomen, especially stomach and pancreas. In addition to these there is an acute form of pulmonary heart failure resulting from packed pulmonary embolism. The treatment of these conditions will be considered in turn.

Obstructive pulmonary heart failure follows the common pattern of other types of low output failure. The output of the heart in advanced stages tends to be low with a high venous pressure. As there is no interference with air entry into the lungs, there is, theoretically, no difficulty about oxygenation of such blood as passes through the alveoli. The arterial oxygen saturation therefore remains normal. However, in the advanced stages of this variety there may be depression of oxygen saturation. Possibly the uneven flow of blood through various parts of the lungs created by obstructive vascular disease leads to defects in haemo-respiratory exchange. Digitalis is certainly worth a trial in this group but, like severe obstructive valvular disease affecting the left heart, the responses are not likely to be either gratifying or well sustained.

The asphyxial form of cor pulmonale As a result of modern investigation the mode of development of heart failure in emphysema appears to be more complex than was originally thought. Many patients with quite severe emphysema, as indi-

Ischaemic heart disease. This condition responds well in the early stages, responses being comparable with those seen in hypertensive heart failure. A special problem arises in the management of congestive heart failure accompanying a recent acute myocardial infarction. The fear of precipitation of ventricular tachycardia or fibrillation has inhibited many physicians from giving digitalis to such patients. The writer's impression is that the development of dyspnoea and venous congestion in such patients is a clear indication for digitalization and the results in such patients are gratifying: some advise giving digitalis on a background of quinidine administration, as the latter will diminish the chance of precipitation of ventricular tachycardia.

Valvular heart disease. Taken as a group, patients who have developed cardiac failure as a result of valvular narrowing or incompetence do not make the same satisfactory clinical responses as patients with hypertensive or ischaemic heart disease. Clinical improvement must be gauged against some knowledge of the natural history of each valvular disease. Once patients with aortic stenosis and aortic incompetence have developed heart failure the course is usually fairly rapidly downhill if systemic venous congestion is present. It would appear at this stage that the valvular trouble imposes a burden from which no relief is possible In mitral stenosis the natural history of the disease has an extraordinary number of variations and the digitalis responses are equally varied. Sometimes they are striking and satisfactory, and on other instances only small degrees of benefit are achieved the increases in cardiac output which result from digitalization are often small, but, none the less, the patients may continue to lead somewhat restricted lives over long periods of years

Acute nephritis We have confirmed the experience of La Due that the venous pressure is raised in practically all instances of acute nephritis and settles with recovery.[78] It has been noted that this raised venous pressure may not fall with digitalization, but this is not universally applicable. We have encountered instances where cardiac failure has become really serious, and in such cases

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cated by high residual air values, may have quite normal pulmonary artery pressures. The pressures, however, do tend to rise more readily on exercise, indicating what Hickam and Cargill[23] call 'rigidity' of the pulmonary vascular bed. When such patients develop acute exacerbations of their bronchitis the arterial oxygen saturation may fall quite severely, and accompanying this the pulmonary artery pressure rises to very high levels. It is possible, also, that super-added asthma may be accompanied by some pulmonary vascular constriction. Diminution of oxygen in the arterial blood also calls for an increase of cardiac output, and no doubt the increased work of the heart combined with a poor oxygen supply involving the myocardium as well as other tissues also play a part in the production of cardiac failure.

In this asphyxial type the patients are noted to have warm hands and bounding peripheral pulses, although in the most advanced stages, often with a falling blood pressure, the circulation may be depressed to minute volume figures below the normal. The condition remains peculiarly intractable. We have favoured oxygen tents as being the most rational approach in these patients. Digitalis is certainly extremely disappointing. It may reduce the venous pressure, but cardiac output improvement is often absent and, in fact, the cardiac output may fall.[4] Rises in cardiac output have, however, been recorded by Cournand and his co-workers even in the high output stages, but the responses were small and of doubtful significance.[20] With my colleagues in this school we have only obtained rises in cardiac output in the advanced low output stages. In the earlier stage, with raised cardiac output, increases have been observed with ouabain. The old clinical observations of Vaquez and Lutembacher[60] indicated that it was in this group of conditions particularly that digitalis would fail, but that ouabain might sometimes initiate a slight clinical success. Wollenberger[74a] draws attention to pharmacological experiments which indicate a poor digitalis response in heart failure induced by anoxia. This may have some bearing on the generally poor responses in 'cor pulmonale' and in anaemic heart failure. If one of the important actions of digitalis is to

increase oxygen utilization by the heart,[26] it is understandable that it might be expected to fail if there was little or no more oxygen available in the coronary blood. This is conceivable in anaemia and emphysema.

Acute cor pulmonale. When the venous pressure is raised as a result of packed pulmonary embolism the clinical picture usually resembles that of shock. The patient's blood pressure has fallen and the pulse is of poor volume. The output of the left heart is presumably low, reduced in a manner similar to that of haemorrhage. The pressure of blood in the great veins near the heart is increased and the right heart is under strain working against increased resistance in the pulmonary vascular bed. So far as the heart is concerned we have hitherto adopted a policy of non-interference. If the patient survives adaptation occurs by ordinary physiological means and ultimately the pulmonary emboli are organized and presumably slowly absorbed. It is just possible that there may in some instances occur a stage in which a fatal issue might conceivably be averted by some form of cardiac stimulation. Since conditions here may so closely resemble those produced by sudden overloading of a previously normal heart, rapidly acting ouabain may be of value, but this is simply speculation.

Pericardial disease, as a cause of cardiac failure, is uncommon but important. The heart is embarrassed by being held in a rigid case of fibrous tissue often calcified. It is prevented from contracting fully by this external mechanical case. Digitalis therapy is of little or no value, changing, as a rule, neither the output nor the pressure The treatment is surgical, and may be phenomenally successful.

Congenital heart disease is only rarely a cause of failure. The blue varieties are embarrassed by poor oxygen supply to their peripheral tissues. In some instances with an overload on the right heart from severe pulmonary stenosis, failure may develop. Digitalis therapy is likely to be disappointing.

Paroxysmal acute left ventricular failure. This dramatic development in patients with hypertensive ischaemic heart disease and

cated by high residual air values, may have quite normal pulmonary artery pressures. The pressures, however, do tend to rise more readily on exercise, indicating what Hickam and Cargill[22] call 'rigidity' of the pulmonary vascular bed. When such patients develop acute exacerbations of their bronchitis the arterial oxygen saturation may fall quite severely, and accompanying this the pulmonary artery pressure rises to very high levels. It is possible, also, that super-added asthma may be accompanied by some pulmonary vascular constriction. Diminution of oxygen in the arterial blood also calls for an increase of cardiac output, and no doubt the increased work of the heart combined with a poor oxygen supply involving the myocardium as well as other tissues also play a part in the production of cardiac failure.

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patient's own inclination to stand up when he gets an attack is equal to a physiological venesection, blood being pooled in the

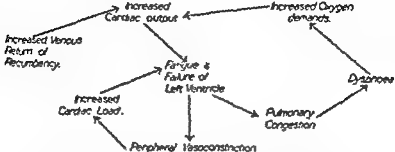

FIG 24 Scheme of the sequence of events in the development of left ventricular failure in recumbency It is not yet certain how the rise in arterial pressure takes place during attacks of left ventricular failure It may be reflex from pressor receptors in the neighbourhood of the failing heart.

lower half of the body. Venesection, however, can be a messy procedure, and in the unexpected emergency it is not likely to be undertaken as frequently as it should The real sovereign remedy is morphine. Exactly how this breaks the vicious circle it is difficult to say We have seen morphine succeed when theophylline has failed. Respiratory depression possibly plays a part together with diminution of the patient's apprehension The pressure in the right heart falls, the arterial pressure also subsides, the left heart recovers from the strain and the pulmonary oedema disappears. In the follow-up treatment after the attack, digitalization, of course, is necessary and once maintenance dosage has been established the frequency of these attacks will be greatly reduced. The régime of mercurial diuretics recommended by Gold and his associates is also of great value in this particular type of cardiac failure.

aortic valvular disease presents many phenomena of great interest. If the patient has been recumbent he suddenly becomes aware of intense dyspnoea or suffocation. He sits up struggling for breath, and in a severe attack may insist on standing up out of bed. The face becomes pale and is often sweating, the extremities are pallid and cold, sometimes blue. The blood pressure always rises in the attack. Along with this the venous pressure nearly always seems to be raised on inspection of the neck veins. In extreme cases gross pulmonary oedema develops with audible moisture at the bases or all over the lungs with the expectoration of frothy and even blood-stained sputum. There is a variety of opinion as to whether this condition is accompanied by any bronchial spasm. Breathing is often audibly wheezy at the bedside, but on auscultation over the lungs sibili are nearly always absent. It is quite possible that some degree of bronchial obstruction results from congestion of the bronchial walls through the anastomoses between the pulmonary and bronchial vascular systems. We have had opportunities to study such attacks when the cardiac catheter has been *in situ*. Although the arteriovenous oxygen difference increases which, other things being equal, would be reflected in a decreased cardiac output, it is possible that the increased metabolism in the dyspnoeic phase may, by increasing oxygen consumption, actually determine a rise in cardiac output above the preceding level The whole cardiovascular storm is certainly initiated by left ventricular failure, dyspnoea making further demands on the heart with a possible small cardiac output increase, and a vicious circle is thereby created (Fig. 24)

In treatment these mechanisms have to be kept in mind, and it is important to emphasize that full intravenous doses of ouabain or digoxin may, from their hypertensive action, temporarily make the condition worse. For this reason full doses are best avoided Among the direct cardiac remedies which have been studied in preceding chapters theophylline-ethylene-diamine is the best but, as stated there, it must be injected slowly or its respiratory stimulating action may cause the patient to feel more dyspnoeic Probably venesection is a better method of treatment and the

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